REMARKS/ARGUMENTS

Applicants thank the Examiner and her supervisor for conducting an interview on February 9, 2005 with applicants' attorneys and co-inventor Dr. Cary Queen. Applicants noted that the Riechmann reference cited in the present office action had been extensively considered in prosecution of predecessor patents and summarized the distinctions that were drawn in prosecution of the predecessor patents. Applicants also explained that the recitation in many of the current claims that amino acids from the donor immunoglobulin framework replace corresponding amino acids from the acceptor immunoglobulin framework requires that the donor amino acid be different that the corresponding acceptor amino acid. The reasons for this construction will be restated below in response to the pending rejection. Applicants also provided further support that the term "consensus" sequence was and is understood in the art to denote the sequence formed from the most frequently occurring amino acids (or nucleotides) in a family of related sequences. The details of applicants' position will be restated below in addressing the relevant rejection in the office action. The Examiner and her Supervisor indicated that if applicants made clear the claim constructions in the record and reasons therefor, they would reconsider the art rejections. Finally, the rejection under 35 USC 112, second paragraph was briefly discussed and the Examiner indicated she would withdraw this rejection.

In accordance with the distinctions drawn over Riechmann at the interview and the terminology used in predecessor patent claims (see e.g., US 5,585,089, all claims, US 5,693,761, claims 11, 28 , 31, 32 and 37, and US 6,180,370, claim 11), present independent claims 108, 110 and 112 have been amended to specify the donor amino acids replace corresponding acceptor amino acids outside the Kabat and Chothia CDRs. As was discussed at the interview, Riechmann's replacement of amino acids at positions H27 and H30 occurs outside Kabat CDR H1 but within Chothia CDR H1. Claim 116 has been amended to clarify the phrase "acceptor immunoglobulin variable region framework is a consensus framework from many human amino acids" refers to the acceptor framework from both heavy and light chains. Such is consistent with the definition of humanized immunoglobulins at p. 14, third paragraph in which humanized immunoglobulins comprising heavy and light chains are described as having "a

human framework." Dependent claims 118, 121, 136, 173, 182, 192 and 202 have been rendered redundant by previous amendment of independent claims and have been cancelled. In some instances the term "donor" or "acceptor" has been amended to donor immunoglobulin or acceptor immunoglobulin for improved antecedent basis. No amendment should be construed as acquiescence in any ground of rejection.

Applicants now turn to the specific issues raised in the office action using the paragraph numbering of the office action.

10-13. Applicants provide a terminal disclaimer over cited patents US 6,180,370, US 5,530,101, US 5,693,762 and US 5,585,089. In an abundance of caution US 5,693,761 is included in the terminal disclaimer. The provision of a terminal disclaimer should not be construed as acquiescence in the merits of the rejection.

14. Claims 125 and 129 stand rejected under 35 USC 112, second paragraph as allegedly indefinite on the basis the phrase "heavy chain variable region framework whose sequence is a consensus sequence of human heavy chain variable region framework sequences" might be interpreted as a concatenation of many heavy chain variable region frameworks. As discussed in more detail at the interview and below, a consensus sequence has a well-known meaning in the art, and does not refer to a concatenation of many heavy chain variable region frameworks. The Examiner said at the interview she would not maintain this rejection.

15. Claims 118, 121, 136, 173, 182, 192 and 202 stand rejected as not further limiting the claim from which they depend. These claims have been cancelled.

16. Claims 108, 110, 112-115, 133, 134, 136, 137, 139-141, 143-148, 153, 154, 156-158, 161, 162, 164, 165-168, 170, 171, 173-180, 182-187, 189, 190, 192, 197, 208 and 209 stand rejected as allegedly anticipated by Riechmann. The Examiner alleges the limitation "amino acids from donor immunoglobulin replace the corresponding amino acids in the acceptor immunoglobulin" renders the claims product-by-process claims. The Examiner takes the

position that if the prior art teaches corresponding amino acids that are same between a donor and acceptor, then such donor amino acids can be viewed as replacing corresponding acceptor amino acids as claimed. The Examiner alleges Riechmann teaches several positions at which the donor amino acid is the same as a corresponding acceptor amino acid. This rejection is respectfully traversed.

The rejection is based on the notion that a donor amino acid can be viewed as replacing an acceptor amino acid even though the two are one and the same amino acid. Applicants respectfully submit this is not a reasonable position given the disclosure of the specification, the phrasing of the claims, and the fact that the prosecution history of the present case will leave no doubt how the term "replace" is to be construed. The specification provides many figures in which replacement amino acids are specifically identified by double underlining (or in some figures asterisks). For example, Figs. 1A and 1B show the donor (upper) and acceptor (lower) amino acid sequences for the light and heavy chains of humanized antibody anti-Tac. Replacement amino acids are shown by double underlining. Only framework amino acids that differ between donor and acceptor are double underlined. Many other figures illustrate the same point (see e.g., Figs. 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5B, 6A, 6B). In no case are amino acids that are the same between donor and acceptor indicated to be replacement amino acids. The criteria for replacement amino acids also require the donor amino acid be different than the acceptor amino acid it replaces.

> Regardless of how the acceptor immunoglobulin is chosen, high affinity may be achieved by selecting a small number of amino acids in the framework of the humanized immunoglobulin chain to be the same as the amino acids at those positions in the donor *rather than* in the acceptor.
>
> By replacing an *unusual amino acid* with an amino acid from the donor antibody that happens to be *typical* for human antibodies, the humanized antibody may be made less immunogenic [an unusual amino acid must be different than a typical one].
>
> In the positions immediately adjacent to one or more of the 3 CDR's in the primary sequence of the humanized immunoglobulin

> chain, the donor amino acids(s) *rather than* acceptor amino acid may be selected.
>
> At those amino acid positions, the donor immunoglobulin amino acid *rather than* the acceptor immunoglobulin amino acid may be selected.
>
> Substitute specification at pp. 16-17 (emphasis supplied).

The context in which the term "replace" is used in the claims also indicates that the term requires the donor amino acid to be different from the corresponding acceptor amino acid. Contrary to the position stated in the office action, the term "replace" does not indicate a process step. No step is actually performed in which an amino acid from a donor antibody is excised from the donor and physically introduced into the acceptor framework. Rather the phrase "replace" is a description of the composition of the humanized antibody. The term describes the humanized antibody by requiring position(s) in the humanized antibody to be occupied by donor amino acids rather than acceptor amino acids.

For these reasons, the specification, wording of the claims and present file history all indicate the term "replace" should be construed as describing a donor amino acid different from a corresponding acceptor amino acid. In light of this construction, all of the above claims are distinguished from Riechmann as discussed detail below.

Riechmann discusses a humanized antibody (Campath) in which one or two acceptor amino acids outside the Kabat CDR H1 but still within Chothia CDR H1 were replaced. Specifically, these replacements occurred at positions H27 and H30. No replacements of amino acids outside both the Kabat and Chothia CDRs are described by Riechmann.

Independent claims 108, 110, and 112 are distinguished in that they require at least three donor amino acids replace corresponding acceptor amino acids outside the Kabat and Chothia CDRs. Riechmann performs only *two* replacements of acceptor amino acids at positions H27 and H30, and these are both *within* Chothia CDRH1.

Independent claims 133, 170 and 189 specify a donor amino acid replaces a corresponding acceptor amino acid at one of several specified positions. None of these positions is H27 or H30, which are the only replacement positions discussed by Riechmann.

Independent claim 178 specifies a donor amino acid replaces a corresponding acceptor amino acid in the acceptor immunoglobulin light chain framework. By contrast, the H27 and H30 replacements discussed by Riechmann occur in the heavy chain.

17. Claims 116, 118, 119, 121-124, 198-200, 202, 204 and 207 stand rejected under 35 USC 102(a) as allegedly anticipated by Riechmann as evidenced by Waldmann US 5,846,534. Waldmann is cited as providing further explanation of the light chain acceptor sequence used by Riechmann. This rejection is respectfully traversed.

Applicants explained in their previous response (and in prosecution of predecessor patents) that the term consensus sequence was and is understood in the art to denote the sequence formed from the most frequently occurring amino acids (or nucleotides) in a family of related sequences. Specifically, in a family of proteins, each position in the consensus sequence is occupied by the amino acid occurring most frequently at that position in the family. However, the Examiner alleges absent an explicit definition to the contrary she can interpret a consensus sequence or consensus framework as requiring only a few residues to be commonly found in many other immunoglobulins. The Examiner states her interpretation is based in part on the teaching of the specification to substitute a "rare" amino acid with a "typical" amino acid. The Examiner also alleges applicants have provided only a single reference to show the art understanding of the term "consensus sequence."

At the interview, applicants explained that the Examiner's position may be based in part on confusion between two distinct features of the specification. The first feature is the strategy for selection of an acceptor framework as described at p. 15, third paragraph of the substitute specification. This paragraph discloses that the acceptor can be a either a framework from a particular human antibody or a consensus framework of many human antibodies. The second feature is the criteria for replacing certain amino acids within the selected acceptor framework. These criteria are described at p. 16, third paragraph to p. 17 third paragraph of the substitute specification. One of these criteria (category 2) specifies that if an acceptor amino acid is unusual, then it can be replaced by a donor amino acid that is more typical for human sequences. Although other criteria are applicable regardless of whether a particular human

framework or consensus framework is chosen as the acceptor, category 2 is only applicable if a particular human framework is chosen as the acceptor: if a consensus framework is chosen as acceptor, then every amino acid is already typical for human sequences, and category 2 is redundant. Thus, category 2 does not relate to a consensus sequence framework, but rather is a criterion for replacing select amino acids within a framework if the framework is from a particular human antibody, and not a consensus framework.

At the interview, applicants also noted many more dictionaries and textbooks could be cited to illustrate the understanding in the art of the term consensus sequence. For example, the National Library of Medicine MeSH definition reads as follows (emphasis added):

> Consensus sequence: A theoretical representative nucleotide or amino acid sequence in which *each* nucleotide or amino acid is the one which occurs most frequently at that site in the different sequences which occur in nature. The phrase also refers to an actual sequence which approximates the theoretical consensus.

Similarly, the well known text book, Molecular Biology of the Cell (Alberts et al., 3rd Ed1994), at section G-7, states the "consensus sequence shows the nucleotide or amino acid most often found at each position."

Copies of these and other textbook and dictionary definitions illustrating the art understanding of the term consensus sequence are attached.

In view of the additional evidence to illustrate understanding in the art, the clarification regarding the teaching of the specification, and the fact that applicants have stated on the record the meaning of consensus sequence (or consensus framework) in this and the previous response, it is respectfully submitted that this meaning should be accepted, as it was in predecessor cases which also contain claims specifying consensus frameworks (see, e.g., US 5,693,762, claim 20 and US 5,693,761, claim 7).

If the term consensus sequence (or consensus framework) is construed as understood in the art, all of the rejected claims are distinguished over Riechmann. Independent claims 116 (as amended), 119 and 198 all require an acceptor immunoglobulin heavy chain

variable region consensus framework. The heavy chain variable region framework used by Riechmann is from the particular human NEW antibody and not from a consensus sequence. Even if one assumes *arguendo* the acceptor immunoglobulin light chain framework used by Riechmann did have a consensus sequence, such would not constitute an anticipation of the present claims which require a heavy chain variable region consensus framework. It should also be noted that even if the light chain framework used by Riechmann did have a consensus sequence, this would not have provided any motivation to the skilled person to attempt to use a consensus sequence for the heavy chain framework, because all three art-known humanized immunoglobulin heavy chains used the human NEW sequence as an acceptor. Thus, it should be appreciated that there was no teaching in the art of the concept of a humanized antibody comprising a consensus heavy chain.

Claim 116 (particularly as amended), 119 and 198 are distinguished from Riechmann for the additional reason that the claims require that amino acids from the donor immunoglobulin framework replace corresponding amino acids from the acceptor immunoglobulin framework having a consensus sequence. If the Phe's introduced at positions H27 and H30 by Riechmann are considered to be part of the acceptor framework, then they cannot also constitute replacements of that framework by donor amino acids. There are no other positions outside the CDR's in Riechmann's humanized antibody occupied by a donor amino acid that replaces (i.e., is different from) the corresponding acceptor amino acid.

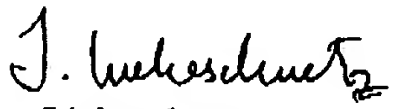
For these reasons, it is respectfully submitted the rejection should be withdrawn.

Other matters

A change of inventorship under 37 CFR 1.48(b) is attached.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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